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(54) **POLYHYDROXYALKANOATE MEDICAL TEXTILES AND FIBERS**

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(57) **ABSTRACT**

Absorbable polyester fibers, braids, and surgical meshes with prolonged strength retention have been developed. These devices are preferably derived from biocompatible copolymers or homopolymers of 4-hydroxybutyrate. These devices provide a wider range of in vivo strength retention properties than are currently available, and could offer additional benefits such as anti-adhesion properties, reduced risks of infection or other post-operative problems resulting from absorption and eventual elimination of the device, and competitive cost. The devices may also be particularly suitable for use in pediatric populations where their absorption should not hinder growth, and provide in all patient populations wound healing with long-term mechanical stability. The devices may additionally be combined with autologous, allogenic and/or xenogenic tissues to provide implants with improved mechanical, biological and handling properties.

19 Claims, 3 Drawing Sheets

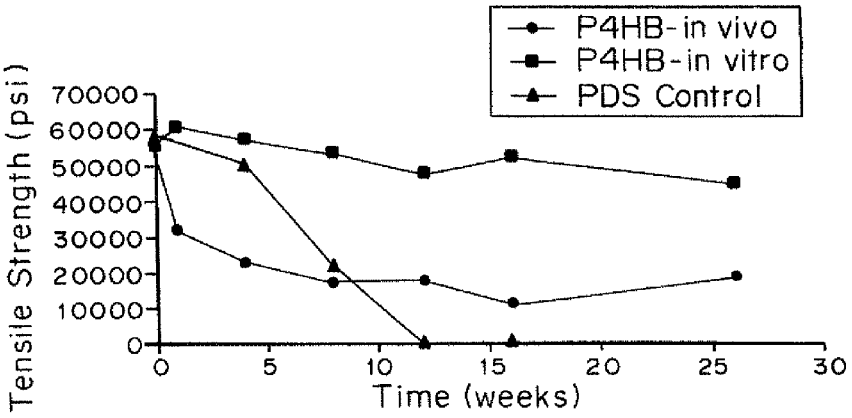

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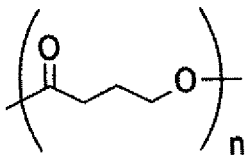
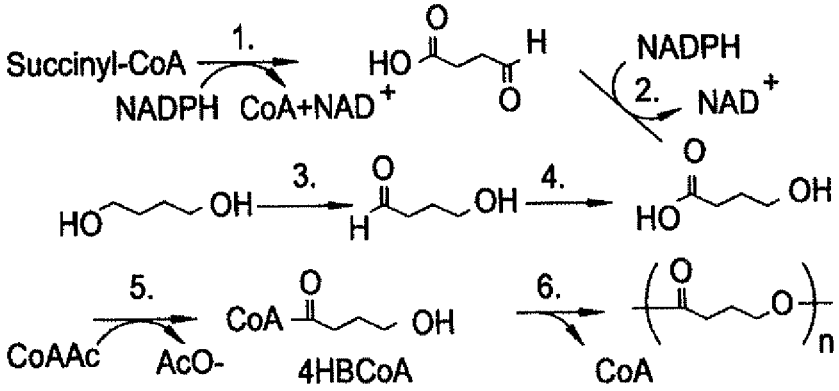
FIG. 1



PRIOR ART

FIG. 2



PRIOR ART

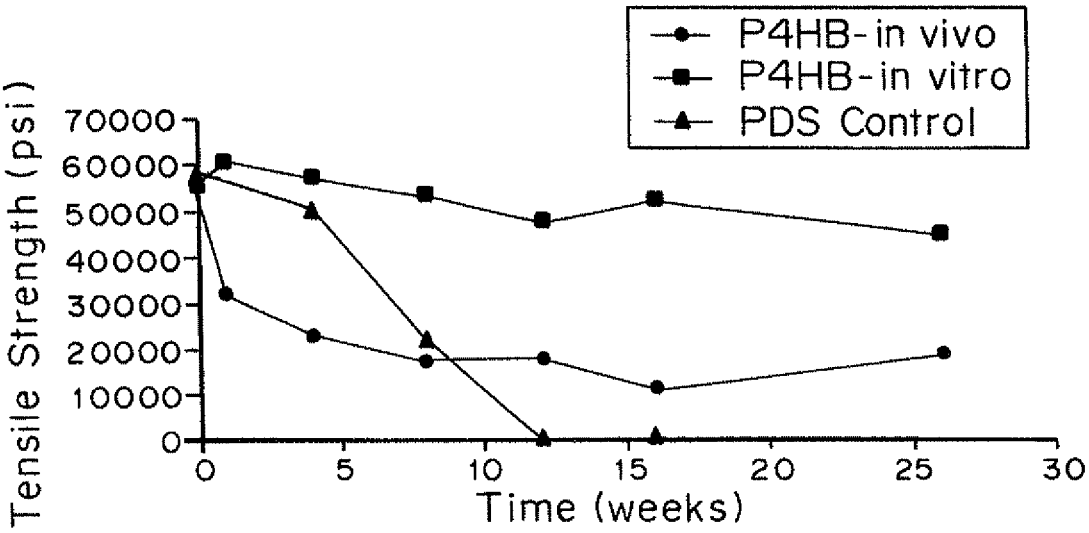

P4HB-in vivo
P4HB-in vitro
PDS Control
Tensile Strength (psi)
70000
60000
50000
40000
30000
20000
10000
0
0
5
10
15
20
25
30
Time (weeks)

FIG. 3

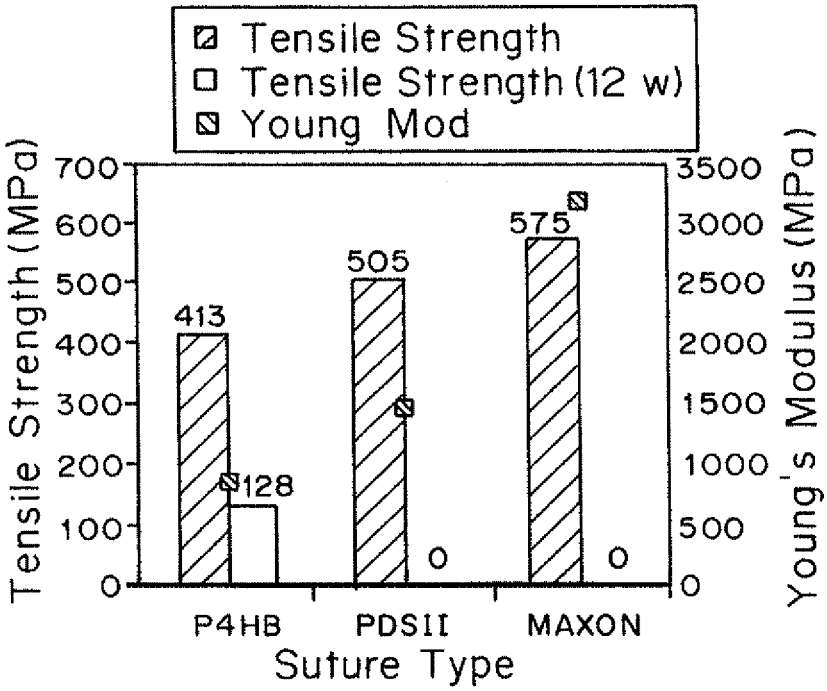

Tensile Strength
Tensile Strength (12 w)
Young Mod
Tensile Strength (MPa)
700
600
500
400
300
200
100
0
3500
3000
2500
2000
1500
1000
500
0
Young's Modulus (MPa)
413
128
505
0
575
0
P4HB
PDSII
MAXON
Suture Type

FIG. 4

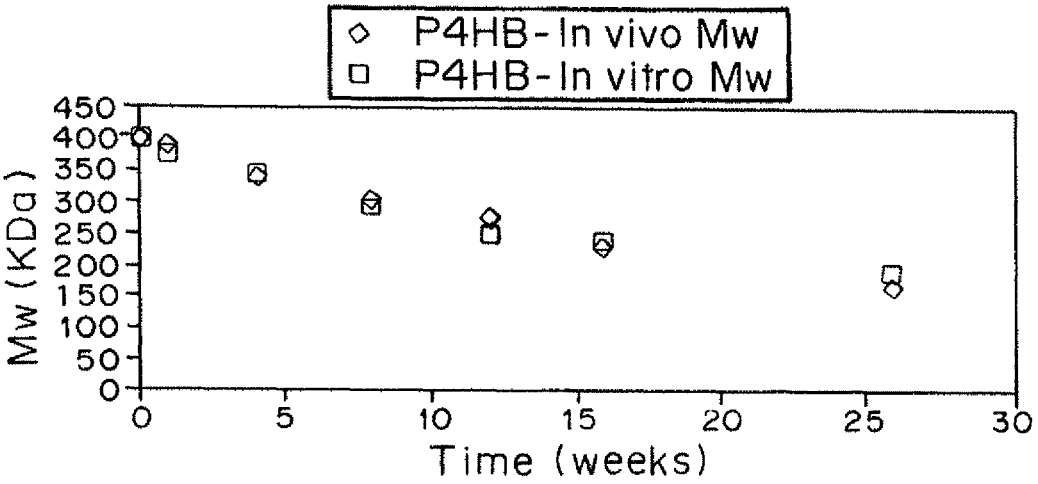

P4HB-In vivo Mw
P4HB-In vitro Mw
Mw (KDa)
450
400
350
300
250
200
150
100
50
0
0
5
10
15
20
25
30
Time (weeks)

FIG. 5

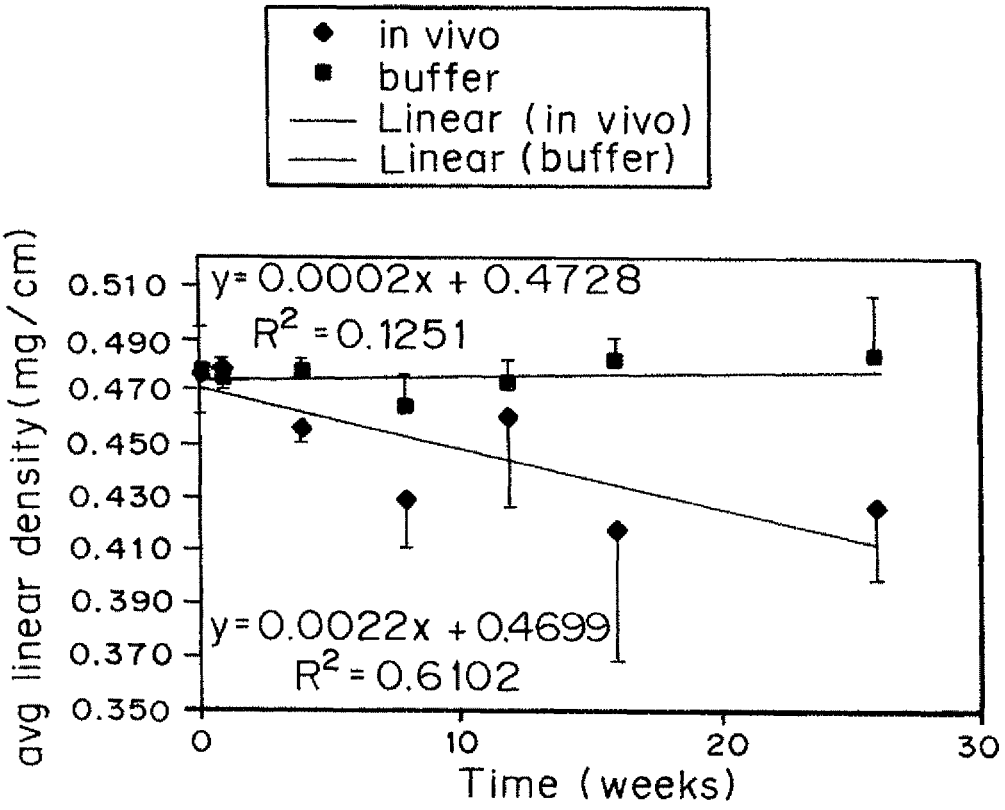

in vivo
buffer
Linear (in vivo)
Linear (buffer)
y = 0.0002x + 0.4728
R2 = 0.1251
y = 0.0022x + 0.4699
R2 = 0.6102
avg linear density (mg/cm)
0.510
0.490
0.470
0.450
0.430
0.410
0.390
0.370
0.350
0
10
20
30
Time (weeks)

FIG. 6

POLYHYDROXYALKANOATE MEDICAL TEXTILES AND FIBERS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a divisional of pending prior application U.S. Ser. No. 10/835,926 filed Apr. 30, 2004, entitled "Polyhydroxyalkanoate Medical Textiles and Fibers" by David P. Martin, Said Rizk, Ajay Ahuja and Simon F. Williams, which claims priority to U.S. Ser. No. 60/563,096 filed Apr. 16, 2004; U.S. Ser. No. 60/545,771 filed Feb. 19, 2004; U.S. Ser. No. 60/534,065 filed Jan. 2, 2004; and U.S. Ser. No. 60/469,469 filed May 8, 2003, all of which are hereby incorporated by reference in their entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with U.S. government support under agreement number 70NANB2H3053 awarded by the U.S. Department of Commerce and grant number 1R43GM64863-01 awarded by the National Institutes of Health Small Business Innovation Research to Tepha, Inc. The U.S. government has certain rights in the invention.

BACKGROUND OF THE INVENTION

The present invention generally relates to textile and fiber-based medical devices derived from poly-4-hydroxybutyrate and its copolymers.

Poly-4-hydroxybutyrate (available from Tepha, Inc., Cambridge, Mass. as PHA4400) is a strong pliable thermoplastic that is produced by a fermentation process (see U.S. Pat. No. 6,548,569 to Williams et al.). Despite its biosynthetic route, the structure of the polyester is relatively simple (FIG. **1**). The polymer belongs to a larger class of materials called polyhydroxyalkanoates (PHAs) that are produced by numerous microorganisms, Steinbüchel, A. Polyhydroxyalkanoic acids, *Biomaterials,* 123-213 (1991); Steinbüchel A., et al. Diversity of Bacterial Polyhydroxyalkanoic Acids, *FEMS Microbial. Lett.* 128:219-228 (1995); and Doi, Y. *Microbial Polyesters* (1990). In nature these polyesters are produced as storage granules inside cells, and serve to regulate energy metabolism. They are also of commercial interest because of their thermoplastic properties, and relative ease of production. Several biosynthetic routes are currently known to produce poly-4-hydroxybutyrate, as shown in FIG. **2**. Chemical synthesis of poly-4-hydroxybutyrate has been attempted, but it has been impossible to produce the polymer with a sufficiently high molecular weight necessary for most applications, Hori, Y., et al. Chemical Synthesis of High Molecular Weight poly(3-hydroxybutyrate-co-4-hydroxybutyrate, *Polymer* 36:4703-4705 (1995).

Tepha, Inc. (Cambridge, Mass.) produces PHA4400 and related copolymers for medical use, and has filed a Device Master Files with the United States Food and Drug Administration (FDA) for PHA4400. Related copolymers include 4-hydroxybutyrate copolymerized with 3-hydroxybutyrate or glycolic acid (U.S. Ser. No. 60/379,583 to Martin & Skraly, U.S. Pat. No. 6,316,262 to Huisman et al., and U.S. Pat. No. 6,323,010 to Skraly et al.). Tepha has also filed a Device Master File with the United States FDA for copolymers containing 3-hydroxybutyrate and 4-hydroxybutyrate. Methods to control molecular weight of PHA polymers have been disclosed by U.S. Pat. No. 5,811,272 to Snell et al., and methods to purify PHA polymers for medical use have been disclosed by U.S. Pat. No. 6,245,537 to Williams et al. PHAs with degradation rates in vivo of less than one year have been disclosed by U.S. Pat. No. 6,548,569 to Williams et al. and PCT WO 99/32536 to Martin et al. The use of PHAs as tissue engineering scaffolds has also been disclosed by U.S. Pat. No. 6,514,515 to Williams, and other applications of PHAs have been reviewed in Williams, S. F., et al. Applications of PHAs in Medicine and Pharmacy, in Biopolymers, *Polyesters, III* Vol. 4:91-127 (2002).

In the practice of surgery there currently exists a need for absorbable fibers and surgical meshes with improved performance. For example, there is currently a need for an absorbable monofilament fiber with a prolonged strength retention that can be used as a suture material. Such a product would potentially be useful in the treatment of patients with diabetes, obesity, nutritional impairment, compromised immune systems, or other conditions such as malignancy or infection that compromise wound healing.

There also exists a need for improved surgical meshes. For example, an absorbable hernia mesh with prolonged strength retention could have many advantages over the non-absorbable synthetic meshes currently used in hernia operations (Klinge, U., et al., Functional Assessment and Tissue Response of Short- and Long-term Absorbable Surgical Meshes, *Biomaterials* 22:1415-1424 (2001). Long-term implantation of these non-absorbable meshes is not considered ideal because they can lead to complications such as adhesions (fistula formation), pain, and restriction of physical capabilities (Klinge et al., 2001). If implanted into surgical sites that are contaminated or have the potential to become contaminated, 50-90% of these non-absorbable implants will need to be removed (Dayton et al. 1986). These implants are also not ideal for use in pediatric patients where they could hinder growth (Klinge et al., 2001). To date, the use of absorbable synthetic surgical meshes in hernia repair has been found to almost invariably result in large incisional hernias that require revision operations because of the relatively short-term strength retention of these materials (Klinge et al., 2001). However, it is thought that an absorbable hernia mesh with prolonged strength retention could solve this problem providing a mechanically stable closure, reduce the incidence of adhesions and risks of infection, and be suitable for use in pediatric patients.

In addition to the need for improved meshes for hernia repair, there are also needs for improved meshes and patches for other procedures. In pericardial repair there exists a need for a surgical material that will prevent adhesions between the sternum and heart following open-heart surgery. There are also similar needs to prevent adhesions in spinal and gynecology procedures that could be addressed with improved surgical meshes and patches.

Biomaterial patches derived from animal and human tissue are currently used fairly extensively in cosmetic surgery, cardiovascular surgery, general surgery (including hernia repair), and in urology and gynecology procedures for the treatment of conditions that include vaginal prolapse and urinary incontinence. There is however reported to be growing concern about the use of animal and human derived biomaterials because of the risks associated with disease transmission. Synthetic absorbable meshes and patches that may offer decreased risks of disease transmission are currently limited, can be inflammatory, and do not provide prolonged strength retention. Thus there currently exists a need to develop new absorbable meshes for these procedures as well. Ideally, these products should have prolonged strength retention, induce minimal inflammatory responses that resolve, provide mechanically stable reinforcement or closure, offer

anti-adhesion properties (where necessary), minimize the risks of disease transmission, and after absorption leave a healthy natural tissue structure.

There is thus a need to develop absorbable fibers with prolonged strength retention that could be used as suturing materials, or in surgical meshes. The latter, offering longer-term mechanical stability, could also be used in other procedures such as pelvic floor reconstruction, urethral suspension (to prevent stress incontinence using the mesh as a sling), pericardial repair, cardiovascular patching, cardiac support (as a sock that fits over the heart to provide reinforcement), organ salvage, elevation of the small bowel during radiation of the colon in colorectal cancer patients, retentive devices for bone graft or cartilage, guided tissue regeneration, vascular grafting, dural substitution, nerve guide repair, as well as in procedures needing anti-adhesion membranes and tissue engineering scaffolds. Strong absorbable fibers could also find other uses, for example, in synthetic ligament and tendon devices or scaffolds. Further uses include combinations with other synthetic and natural fibers, meshes and patches. For example, the absorbable fibers and devices such as meshes and tubes derived from the fibers could be combined with autologous tissue, allogenic tissue, and/or xenogenic tissues to provide reinforcement, strengthening and/or stiffening of the tissue. Such combinations could facilitate implantation of the autologous, allogenic and/or xenogenic tissues, as well as provide improved mechanical and biological properties. Combination devices could be used for example in hernia repair, mastopexy/breast reconstruction, rotator cuff repair, vascular grafting/fistulae, tissue flaps, pericardial patching, tissue heart valve implants, bowel interposition, and dura patching.

It is therefore an object of this invention to provide absorbable fibers, surgical meshes, and medical devices with one or more of the following features: prolonged strength retention in vivo, anti-adhesion properties, minimal inflammatory reaction upon implantation, minimal risk for disease transmission or to potentiate infection, remodeling in vivo to a healthy natural tissue.

It is another object of this invention to provide methods for fabricating the articles and devices with prolonged strength retention.

It is yet another object of the invention to provide absorbable multifilament fibers, and methods for fabricating these multifilaments into surgical meshes.

It is still yet another object of the invention to combine the fibers and meshes with autologous, allogenic and/or xenogenic tissues to provide improved mechanical, biological and handling properties of the autologous, allogenic and/or xenogenic tissues.

SUMMARY OF THE INVENTION

Absorbable polyester fibers, braids, and surgical meshes with prolonged strength retention have been developed. These devices are preferably derived from biocompatible copolymers or homopolymers of 4-hydroxybutyrate. These devices provide a wider range of in vivo strength retention properties than are currently available, and offer additional benefits such as anti-adhesion properties, reduced risks of infection or other post-operative problems resulting from absorption and eventual elimination of the device, and competitive cost.

The devices are also particularly suitable for use in pediatric populations where their absorption should not hinder growth, and provide in all patient populations wound healing with long-term mechanical stability. The devices may additionally be combined with autologous, allogenic and/or xenogenic tissues to provide implants with improved mechanical, biological and handling properties.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is the chemical structure of poly-4-hydroxybutyrate (P4HB, poly-4-hydroxybutyrate).

FIG. **2** shows some of the known biosynthetic pathways for the production of P4HB. Pathway enzymes are: 1. Succinic semialdehyde dehydrogenase, 2. 4-hydroxybutyrate dehydrogenase, 3. diol oxidoreductase, 4. aldehyde dehydrogenase, 5. Coenzyme A transferase and 6. PHA synthetase.

FIG. **3** is a graph of strength retention data of PHA4400 fibers (in vitro and in vivo) compared with PDS™ control fiber (in vivo). ▲(PDS™ control); ●(P4HB sutures-in vivo); ■(P4HB sutures-in vitro).

FIG. **4** is a graph comparing the tensile mechanical properties of PHA4400 and commercially available monofilament sutures.

FIG. **5** is a graph of the degradation of PHA4400 (P4HB) samples in vivo compared to in vitro controls. The Mw (KDa) for implanted (in vivo) and buffer control sutures (in vitro) is plotted versus time. □(P4HB-in vitro Mw); ◇ (P4HB-in vivo Mw)

FIG. **6** is a graph of the ratio of mass and length of the PHA4400 sutures (in vitro and in vivo) plotted as a function of degradation time.

DETAILED DESCRIPTION OF THE INVENTION

Absorbable fibers and meshes with prolonged strength retention have been developed.

I. Definition

Strength retention refers to the amount of time that a material maintains a particular mechanical property following implantation into a human or animal. For example, if the tensile strength of an absorbable fiber decreased by half over 3 months when implanted into an animal, the fiber's strength retention at 3 months would be 50%.

Biocompatible refers to the biological response to the material or device being appropriate for the device's intended application in vivo. Any metabolites of these materials should also be biocompatible.

Poly-4-hydroxybutyrate means a homopolymer comprising 4-hydroxybutyrate units. It may be referred to as P4HB, PHA4400 or TephaFLEX™ biomaterial and is manufactured by Tepha Inc., Cambridge, Mass.

Copolymers of poly-4-hydroxybutyrate mean any polymer comprising 4-hydroxybutyrate with one or more different hydroxy acid units.

II. Source of Poly-4-Hydroxybutyrate and Copolymers Thereof

Tepha, Inc. of Cambridge, Mass. produces poly-4-hydroxybutyrate and copolymers thereof using transgenic fermentation methods.

III. Poly-4-Hydroxybutyrate Fibers with Prolonged Strength Retention

Around 1984, a division of Johnson and Johnson (Ethicon) first introduced a monofilament synthetic absorbable suture known as PDS™, made from polydioxanone. This suture retains about 50% of its strength up to 6 weeks after implantation, and is completely absorbed in the body within 6 months. Davis and Geck subsequently introduced a monofilament suture based on a copolymer of glycolide and trimethylene carbonate that is sold under the tradename of Maxon™. This suture has a similar strength retention to PDS™. Two

other monofilament sutures were introduced more recently. Monocryl™ based on segmented copolymers of glycolide and caprolactone, and Biosyn™ based on a terpolymer of glycolide, p-dioxanone, and trimethylene carbonate. Monocryl™ is reported to have a 20-30% breaking strength after 2-3 weeks, and be completely absorbed after 3-4 months. Biosyn™ has an absorption profile similar to Monocryl™. Despite continued innovation in the development of absorbable synthetic monofilament sutures there is still a need for a synthetic absorbable suture with extended strength retention for patients requiring long-term wound support, for example, a monofilament suture with 50% strength retention at 3-6 months (after implantation). There are also limited options for synthetic absorbable meshes with prolonged strength retention.

U.S. Pat. No. 6,548,569 to Williams et al. discloses that poly-4-hydroxybutyrate has a slower absorption rate in vivo than many materials used as absorbable sutures, and provides absorption data for unoriented poly-4-hydroxybutyrate films and porous samples. It does not, however, disclose the strength retention of fibers of poly-4-hydroxybutyrate following implantation.

It has now been discovered that oriented fibers of PHA4400 and copolymers thereof can be prepared with tensile strengths comparable to existing synthetic absorbable suture fibers (such as PDS™), but have a prolonged strength retention in vivo of over 20-30% at 3-6 months. In comparison, a control PDS suture had little tensile strength remaining after 12-15 weeks.

It has also been discovered that oriented poly-4-hydroxybutyrate fibers can be used to prepare surgical meshes and tubes with prolonged strength retention. These fiber and textile devices may further be combined with autologous, allogenic and/or xenogenic tissues to impart improved properties to these implantable tissues. Properties that can be improved through this combination include mechanical properties such as tensile strength and modulus, for example, to reinforce the tissues to make them stronger, stiffer, more durable, and easier to implant.

Non-limiting examples are given herein to describe the methods for preparing the fibers, meshes, and composite devices with autologous, allogenic and/or xenogenic tissues, and to illustrate the strength retention of the fibers upon implantation.

EXAMPLE 1

Melt Extrusion of PHA4400 to Produce Monofilament Fibers

PHA4400 (Tepha, Inc., Cambridge, Mass.) (Mw 575K) was ground into small pieces using a Fritsch cutting mill (Pulversette 15, 10 mm bottom sieve) and dried under vacuum overnight prior to melt processing. Monofilament fibers of PHA4400 were melt extruded using an AJA (Alex James Associates, Greer, S.C.) ¾" single screw extruder (24:1 L:D, 3:1 compression) equipped with a Zenith type metering pump (0.16 cc/rev) and a die with a single hole spinnerette (0.026", 2:1 L:D). The 4 heating zones of the extruder were set at 140°, 190°, 200° and 205° C. The extruder was set up with a 15 ft drop zone, 48" air quench zone (10° C.), a guide roll, three winders and a pickup. The fiber was oriented in-line with extrusion by drawing it in a multi-stage process to provide fiber with high tensile strength and a reduced extension to break. The fiber was drawn in-line to stretch ratios of 6 to 11×. A spin finish (Goulston, Lurol PT-6A) was dissolved in iso-propanol at 10 vol/vol % and applied to the fiber before the first roll to act as a lubricant and protect the fiber during downstream processing. A series of fibers of different sizes were produced by varying the extrusion conditions (metering pump speed) and drawing conditions (draw ratio). Tensile mechanical properties of the melt extruded fibers were determined using a universal mechanical tester, and results are shown in Table 1. As is evident, the tensile strength of the oriented PHA4400 fiber is comparable to 450-560 MPa reported for the commercial suture fiber, PDS™, Chu, C. C., et al. *Wound Closure Biomaterials and Devices*, CRC Press (1997). The weight average molecular weight (Mw) of the fibers was determined by gel permeation chromatography (GPC) and is also shown in Table 1.

TABLE 1

Properties of melt extruded PHA4400 monofilament.

Sample	Draw Ratio	Diameter (μm)	Load at break (g)	Tensile Strength (MPa)	Elongation to Break (%)	Mw** (K)
1	5.95	125	533	426	107	338
2	5.95	113	274	268	126	293
3	5.95	82	68	126	34	278
4	5.95	128	389	297	134	302
5	6.00	134	426	296	118	313
6	10.75	120	569	494	32	348
7	10.75	120	446	387	29	356
10*	10.75	217	1304	346	70	395
11*	5.95	190	1291	447	135	396

*Note: Samples 10 and 11 were spun through a larger spinnerette (0.045", 2:1 L:D).
**Note Mw of starting polymer was 575 K.

EXAMPLE 2

Strength Retention and Biocompatibility of PHA4400 Monofilament Fibers

An implantation study to determine the strength retention of PHA4400 fibers was undertaken in a rabbit model. Sample 10 (shown in Table 1) was selected for these studies because the fiber had an elongation to break of 70% and tensile strength of 346 MPa (60,000 psi) that is comparable to commercial monofilament absorbable sutures. Prior to implantation the fiber was sterilized using cold ethylene oxide gas (40° C., ethylene oxide pressure of 13.7 INHGA, humidity of 1.7 INHGA, dwell time 4 hr, and aeration time 10 hr). A small amount of fiber shrinkage (2%) was noted to result during the sterilization process. A commercial monofilament absorbable suture material, PDS™, was used as a control.

Under sterile conditions, the sterilized sutures were placed perpendicular to the dorsal midline of the rabbit. After making a small incision, a large hemostat was introduced through the incision into the subcutaneous tissue and tunneled approximately 9 inches into the subcutis layer. The PHA4400 and control (3/0 PDS™) suture fibers were threaded individually through separate surgically created implant areas and left in place. The incisions were closed with tissue glue. A total of four test and four control samples were implanted in each rabbit. Animals were maintained for periods of 1, 4, 8, 12, 16 and 26 weeks (2 rabbits per time point) and were observed daily to ensure proper healing of the implant sites. At the end of the appropriate time points, the animals were weighed and euthanized by an injectable barbituate. Tissue sections containing the implanted sutures were excised from the animals. One test and one control sample were fixed in formalin and retained for histological analysis of the tissue surrounding the suture implants. The remaining three samples from each

group were cleaned of tissue, wrapped in sterile, saline soaked gauze and returned on the day of explantation for further analysis. Suture samples were further cleaned of residual tissue and dried.

In parallel with the in vivo degradation study, an in vitro degradation study was conducted to generate comparative data. Sterilized PHA4400 monofilament fibers, identical with those used in the implantation study, were incubated in Dulbeco's phosphate buffered saline (pH 7.4, 37° C.) containing sodium azide (0.05%) as a preservative. Six control PHA4400 sutures per time point were enclosed in sterile polyethylene sample bags and removed at the same time as each of the implant samples. The in vivo and in vitro samples were processed identically.

Strength Retention

The explanted suture samples were subject to tensile testing according to the procedure of ASTM D2256-97. The results of this tensile testing are shown in FIG. **3**. As can be seen, the PHA4400 and PDS™ control sutures had very comparable starting tensile strengths (60,000 psi). As expected, the PDS™ control sutures maintained 50% of their initial tensile strength until approximately the 6^{th} week. In contrast, the implanted PHA4400 sutures retained approximately 30% of their tensile strength through the 26^{th} week. A comparison of the tensile mechanical properties of PHA4400 and commercially available monofilament sutures is shown in FIG. **4**.

Unlike the implanted suture, the PHA4400 in vitro control suture showed a more gradual loss of strength during the entire 26-week degradation study, retaining 80% of its original strength. This result demonstrates the mechanical stability of the polymeric material to simple hydrolysis.

Molecular Weight and Mass Loss

In addition to the strength retention of the PHA4400 suture fibers, the Mw of the PHA4400 samples were analyzed by GPC. As shown in FIG. **5**, the Mw of the implanted and control PHA4400 sutures decreased gradually during the course of the degradation study to approximately 43% of their original Mw at 26 weeks. Additionally, there does not appear to be a significant difference between the Mw of the implanted and the in vitro control PHA4400 sutures. This result shows that the hydrolytic stability of the implanted sample is very similar to the in vitro control.

In order to determine the mass loss of the samples over time, the mass and length of the PHA4400 sutures (in vitro and in vivo) were determined and plotted as a function of degradation time. The ratio of mass to length of the PHA4400 samples (implanted and buffer control) is plotted vs. degradation time and shown in FIG. **6**. The mass/length ratio was determined rather than just the mass of the sample, because this ratio normalizes for samples that were cut during implantation or that break during harvest. As can be seen in this figure, the implanted sutures appear to loose mass more rapidly than the in vitro controls. This data shows that the implanted samples lost mass more rapidly than the in vitro control samples and suggests that surface degradation is occurring in vivo.

Tissue Reaction

The tissue surrounding the implanted PHA4400 and PDS™ control sutures was analyzed for the tissue reaction to the implanted articles through the 26-week time point. Formalin fixed tissue samples (PHA4400 and PDS™ control) from each test animal were sectioned and graded by a board certified veterinarian for the following: inflammation, fibrosis, hemorrhage, necrosis, degeneration, foreign debris and relative size of involved area.

Hisotopathological evaluation indicated that the finding at the PDS™ control and PHA4400 sites were similar and there were no significant indications of a local toxic effect in either the control or the test sites.

EXAMPLE 3

Knitted Mesh of PHA4400 Monofilament Fibers with Prolonged Strength Retention

A warp knitted mesh of PHA4400 was produced from 100 μm diameter oriented monofilament PHA4400 fiber produced as described in Example 1. A warp knit type of construction is desirable as an implant because it can be cut by the surgeon and will not readily unravel. The mesh was fabricated using fiber of 100 μm monofilament PHA4400, tensile strength 92,000 psi, and an elongation to break of 77%. Fabric construction was as follows: Mach #30 Raschel Knit 36 gauge fabric, 150 ends, 16 courses, 40 stitches per inch, using 18 needles per inch. Specifications for the finished fabric were: Weight: 58 g/m^2 (1.72 oz/sq. yard), Thickness: 0.29 mm.

EXAMPLE 4

Extrusion of Suture Fibers of a Copolymer of Glycolate and 4-hydroxybutyrate (PHA4422)

PHA4422 containing 5% glycolic acid comonomer (Mw 305,000 by GPC) was melt extruded into a fiber and converted to a suture as follows. The polymer was prepared by milling the bulk polymer into approximately 1 mm sized particles using a P-15 laboratory cutting mill (Fritsch, Germany) dried in a vacuum desicator. The polymer was extruded using an AJA ⅝" single screw extruder (Alex James and Associates) with a single-hole spinneret (0.040", 2:1 L/D). The extruder had five separate temperature zones that were set to 120, 154, 155, 160 and 160° C. from the inlet to the outlet, with a gear pump at the outlet. The total residence time in the extruder was estimated at 9 minutes.

After extrusion there was a 10 ft drop zone through air before a quenching water bath (5° C.). Following the quench bath, three winders were used to collect the fiber. A first winder was set for a speed of about 2.5 meters per minute. The bath length was about 3-4 ft and the residence time for the fiber in the bath was estimated at about 30 seconds. Crystallization of the fiber occurred before the first winder. Two additional winders (17.5 and 19.5 meters/minute) extended the fiber about 8 times (8× draw). A take up unit was used with only slight tension. Varying the polymer extrusion rate while keeping the downstream orientation and take up rates the same produced fibers of different diameters. Initially, the extruder was set at a gear pump rate of 7, and then successively slowed resulting in fibers of approximately 375, 275 and 200 μm diameter, see Table 2.

Suture needles were attached to each of the different diameter fibers and the sutures were packaged for sterilization. Tensile strength (straight and knot pull) was determined for representative samples of the sutures, see Table 2.

TABLE 2

Physical characterization of sutures prepared by melt extrusion of PHA4422 (5% glycolic acid comonomer, Mw 300K).

Fiber diameter (μm)	Corresponding USP size approx.	Tensile Strength Straight Pull (lbf)	Elongation Straight Pull (%)	Tensile Strength Knot Pull (lbf)	Elongation Knot Pull (in)
375 +/− 6	0	9.2 +/− 1.6	128 +/− 33	4.6 +/− 0.4	51 +/− 4.2
256 +/− 1	2/0	5.3 +/− 0.3	65 +/− 13	3.8 +/− 0.8	49 +/− 18
199 +/− 5	4/0	3.0 +/− 0.3	130 +/− 24	1.6 +/− 0.3	44 +/− 15

EXAMPLE 5

Monofilament Fiber with Peak Tensile Stress of Greater that 70 kg/mm^2

Melt spinning of Poly-4-hydroxybutyrate "PHA4400" polymer has been extremely difficult to accomplish due to melt flow instability and tackiness of resulting fiber. Melt leaving the spinning die exhibited periodic diameter fluctuation and helical structure. These flow irregularities are known as melt fracture or "elastic turbulence" and are generated while the melt is entering and passing through spinneret hole. The reason for such flow irregularities is very high viscosity of the viscoelastic melt and a very high elastic function at the exiting point of spinneret capillary.

The low glass transition temperature of about −50° C., and the low tendency to crystallize of this polymer explain the stickiness of the fibers. In addition to that, the orientation, which was generated during melt spinning, relaxed after a very short time so that the fibers offered a low tenacity for further drawing.

This example illustrates our ability to overcome the above processing problems and produce high strength fiber. PHA4400 polymer was dried to less than 0.01% moisture. Dried pellets of the PHA4400 were fed to an extruder barrel under a blanket of nitrogen. Barrel temperatures zones were kept at 100° C. feed, 150° C. transition and 200° C. metering. Molten polymer passed through a heated block to a metering pump then extruded from a die with a single hole spinneret. The block, metering pump and the die were kept at 220° C. temperature. Pump discharge pressure was kept below 1000 psi by control of temperatures, and the speed of the metering pump. Spun extrudate filament was free from all melt irregularities. The extrudate was allowed dwell time to crystallize after which further multi stage drawing was possible to increase crystal orientation and gain strength. The fiber was then heat treated and rolled on a winding spool. Properties of the ensuing fiber are shown in Table 3.

TABLE 3

Physical characterization of fibers prepared by melt spinning of PHA4400

Fiber Min Diam. microns	Fiber Max Diam. microns	Peak Load kgf	Min Break Strength kgf/mm^2	Min Break Strength PSI	Min Break Strength MPa
0.070	0.089	0.46	73.98	1.05E+05	726
0.129	0.178	1.80	72.37	1.03E+05	710
0.256	0.305	5.50	75.32	1.07E+05	739
0.421	0.470	13.00	74.97	1.07E+05	735
0.523	0.622	22.70	74.74	1.06E+05	733

"Diam" means Diameter

EXAMPLE 6

Monofilament Fibers with Prolonged In Vivo Strength Retention

The PHA4400 monofilaments prepared as in Example 5 were sterilized using cold ethylene oxide gas (40° C., ethylene oxide pressure of 13.7 INHGA, humidity of 1.7 INHGA, dwell time 4 hr, and aeration time 10 hr).

Under sterile conditions, the sterilized monofilament fibers were placed perpendicular to the dorsal midline of the rabbit. After making a small incision, a large hemostat was introduced through the incision into the subcutaneous tissue and tunneled approximately 9 inches into the subcutis layer. The PHA4400 fibers were threaded individually through separate surgically created implant areas and left in place. A total of four test and four control samples were implanted in each rabbit. Animals were maintained for a period of 2 weeks (2 rabbits) and were observed daily to ensure proper healing of the implant sites. At the end of the appropriate time points, the animals were weighed and euthanized. Tissue sections containing the implanted sutures were excised from the animals. Samples were cleaned of tissue, wrapped in sterile, saline soaked gauze and returned on the day of explantation for further analysis. Suture samples were further cleaned of residual tissue and dried. Tensile strength was determined on a universal testing machine. The tensile breaking load of the explanted fiber after 2 weeks implantation was found to be 8.5 lbf peak load, which is 87% of that of the starting fiber (9.8 lbf). Thus these fibers demonstrated a higher strength retention in vivo (87% at 2 weeks) when compared to the fibers in Example 2, FIG. **3** (50% at 2 weeks).

EXAMPLE 7

Multifilament Yarn

Fiber spinning was carried out in the same manner as example 5 except with the die having a multi hole spinneret (20 holes×0.0065 inches). Extrudate yarn was allowed time to crystallize, and a super cooled stream of gaseous media/liquid mist perpendicular to the fiber axis was introduced. A subzero bath was also used and proved a suitable substitute for the gaseous media. The resulting filaments were further processed through cold and heated godets, and the filaments could be oriented and heat set. Yarn tenacity of greater than 3.5 gpd (gram per denier) with 30% elongation was obtained. Representative data for the multifilament yarns is shown in Table 4.

TABLE 4

Tensile properties for PHA4400 multifilament yarns.

Sample	Denier per filament	Peak Load Kg	Strain at break (%)	Tenacity g/denier
1	33.8	2.43	97	3.6
2	27.1	1.69	114	3.1
3	23.7	1.92	58	4.1
4	16.2	1.12	113	3.4
5	12.8	0.99	107	3.9
6	10.3	0.71	74	3.5

EXAMPLE 8

Knitted Fabric from a Multifilament Yarn

A multifilament yarn was knitted into a tube using a single feed, circular weft knitting machine (Lamb Knitting Co., model ST3A/ZA). The width of the flat tube was approximately 9 mm. The yarn knitted very well without evidence of fiber breakage even without the addition of a spin finish as a lubricant. After cleaning and sterilization, the knitted tube appears well suited for use as an absorbable medical fabric.

EXAMPLE 9

Absorbable Polymeric Support Structure for Biological Tissue Implant

PHA4400 fiber woven, knitted or braided into semi rigid support tubes or PHA4400 polymer directly extruded into support tubes can be prepared with an inner diameter closely matching that of a biological substrate implant (e.g. autologous, allogenic and/or xenogenic tissue). The biological implant can be inserted into the support tube, and may optionally be secured in place, for example, by suturing, prior to implantation. The addition of the support tube provides improved strength, modulus, and can make implantation easier. Similarly sheets of extruded film, woven, non-woven or knitted fabric may be rolled over a biological tissue implant and the fabric ends may be tied, sutured or glued to maintain a semi-rigid construct over the biological implant.

A woven tube was produced from 0.300 mm diameter monofilament PHA4400 fiber extruded as described in Example 5. Using circular weaving equipment a 10 mm inside diameter tube was produced. The tube construction allowed insertion of an implant biological substrate and provided enough stiffness to position and suture an otherwise flaccid biological implant.

We claim:

1. An oriented melt extruded polymeric fiber, wherein the polymer consists of a poly-4-hydroxybutyrate homopolymer, wherein the fiber has a tensile strength between a tensile strength greater than 126 MPa and 739 MPa, and wherein the fiber is prepared by a method comprising melt extrusion, allowing the extrudate dwell time to crystallize and drawing the fiber.

2. The fiber of claim **1** wherein the weight average molecular weight of the fiber decreases less than 80% after implantation for 6 months.

3. The fiber of claim **1** wherein the weight average molecular weight of the fiber decreases less than 75% after implantation for 2 weeks.

4. The fiber of claim **1** wherein the tensile strength of the fiber decreases less than 80% after implantation for 6 months.

5. The fiber of claim **1** wherein the tensile strength of the fiber decreases less than 75% after implantation for 2 weeks.

6. The fiber of claim **1** wherein the elongation to break is over 20%.

7. The fiber of claim **1** wherein the fiber is a monofilament, multifilament, or braided structure.

8. A device comprising one or more oriented melt extruded polymeric fibers wherein the polymer consists of a poly-4-hydroxybutyrate homopolymer, having a tensile strength between a tensile strength greater than 126 MPa and 739 MPa, and wherein the fiber is prepared by a method comprising melt extrusion, allowing the extrudate dwell time to crystallize and drawing the fiber, selected from the group consisting of a medical textile, tube, general surgical mesh, hernia mesh, breast reconstruction mesh, mastopexy mesh, pericardial patch, anti-adhesion patch, cardiovascular patch, guided tissue regeneration patch, sling, monofilament suture, multifilament suture, braid, ligament, tendon, meniscus repair device, cartilage repair device, nerve guide, stent, vascular graft, and dura.

9. The device of claim **8** wherein the device is a knitted mesh, woven mesh, or nonwoven mesh.

10. The device of claim **8** wherein the weight average molecular weight of the fiber in the device decreases less than 80% after implantation for 6 months.

11. The device of claim **8** wherein the weight average molecular weight of the fiber in the device decreases less than 75% after implantation for 2 weeks.

12. The device of claim **8** wherein the tensile strength of the fiber in the device decreases less than 80% after implantation for 6 months.

13. The device of claim **8** wherein the tensile strength of the fiber in the device decreases less than 50% after implantation for 2 weeks.

14. The device of claim **8** wherein the breaking strength of the device is at least 10 psi.

15. The device of claim **8** further comprising harvested autologous tissue, allogenic tissue, or xenogenic tissue.

16. The device of claim **15** wherein the device reinforces, supports, strengthens, or stiffens the autologous, allogenic, and/or xenogenic tissues.

17. The device of claim **16** wherein the device stiffens the tissue to facilitate implantation.

18. The device of claim **15** wherein the harvested autologous tissue, allogenic tissue, or xenogenic tissues is selected from the group consisting of vascular grafts, heart valves, pericardium, skin, intestine, muscle, ligament and tendon, cartilage and meniscus, nerves, dura, fascia, and organs.

19. An oriented melt extruded polymeric fiber wherein the polymer consists of a poly-4-hydroxybutyrate homopolymer wherein the fiber is produced by a method comprising drying the polymer, extruding the polymer at a temperature between 100° C. and 220° C., allowing the polymer time to crystallize, and then drawing the polymer to stretch ratios from 6 to 11X at a temperature above the polymer's glass transition temperature.

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